LATE PUBLICATION ABSTRACTS
MONDAY, SEPTEMBER 7, 2015

CLINICAL TRIALS 1
MONDAY, SEPTEMBER 7, 2015 - 10:45-12:15

ORAL11.01 Bevacizumab 15mg/kg Plus Cisplatin-Pemetrexed (CP) vs CP in Malignant Pleural Mesothelioma (MPM): IFCT-GFPC-0701 MAPS Randomized Phase 3 Trial Arnaud Scherpereel[1], Julien Mazières[2], Jacques Margery[3], Laurent Greillier[4], Clarisse Audigier-Valette[5], Denis Moro-Sibilot[6], Olivier Molinier[7], Romain Corre[8], Isabelle Monnet[9], Valérie Gounant[10], Frédéric Rivière[11], Henri Janicot[12], Radj Gervais[13], Chrystele Locher[14], Bernard Milleron[15], Quân Tran[15], Marie Paule Lebitasy[15], Christian Creveuil[16], Jean-Jacques Parienti[16], Franck Morin[15], Gérard Zalcman[16] [1]*Pneumology, CHU Lille, Lille/France,* [2]*Hôpital Larrey, Centre Hospitalier Universitaire de Toulouse, Toulouse/France,* [3]*Gustave Roussy, Villejuif/France,* [4]*Hôpital Nord, Marseille/France,* [5]*Chi Toulon, Toulon/France,* [6]*Pôle Thorax Et Vaisseaux, Unité D'Oncologie Thoracique, Service de Pneumologie,, Grenoble/France,* [7]*Ch Le Mans, Le Mans/France,* [8]*CHU, Rennes/France,* [9]*Chi Créteil, Créteil/France,* [10]*Aphp, Cancerest, Tenon University Hospital, Paris/France,* [11]*Hia Percy, Clamart/France,* [12]*CHU, Clermont-Ferrand/France,* [13]*Centre François Baclesse, Caen/France,* [14]*Ch, Meaux/France,* [15]*French Cooperative Thoracic Intergroup (Ifct), Paris/France,* [16]*CHU, Caen/France*

Background: MPM median overall survival (OS) did not exceed 13 months with pemetrexed-platinum doublet, with virtually no surviving patients at 5 years. Vascular endothelial growth factor is a potent mitogen for MPM cells. **Methods:** In this French multicenter randomized phase 3 trial, eligible patients had unresectable, histologically proved MPM, age < 76, no prior chemo, PS 0-2, no thrombosis, nor bleeding. Randomized patients (1:1) received pem 500 mg/m2, CDDP 75 mg/m2 at D1, with (arm B) or without bevacizumab (arm A), 15 mg/kg Q21D, for 6 cycles. Arm B non-progressive patients received bevacizumab maintenance therapy until progression or toxicity. Primary endpoint was OS. 445 patients were to be randomized, and 385 events observed, to show a significant OS improvement, with 80% statistical power, 5% a-risk. **Results:** From Feb. 2008 to Jan. 2014, 448 patients were included in 73 centers. Males: 75.4%, median age: 65.7 years (range 34.7-75.9), PS 0-1: 96.7%. The IDMC recommended a second interim analysis after 85% of events. On 01-Jan-2015, the duration since last news was < 30 days in 105 out of 106 still living patients. Overall survival was significantly longer in the experimental arm (median: 18.8 months, 95%CI[15.9-22.6] vs. 16.1 months, 95%CI[14.0-17.9] for the reference arm, (adj.HR = 0.76, 95%CI[0.61; 0.94], p = 0.012). With only 46/448 non-progressive patients at the date of analysis, median PFS was 9.6 months, 95%CI[8.5-10.6] in bevacizumab arm vs. 7.5 months, 95%CI[6.8-8.1] (adj.HR = 0.62, 95%CI[0.50-0.75], p < 0.0001). G3-4 hematological toxicities did not significantly differ in the two arms (49.5% vs. 47.3%). Significantly more G3 proteinuria (0.0 vs. 3.1%), G3 hypertension (0.0 vs. 23%), G3-4 arterial thrombotic events (0.0 vs. 2.7%) were observed in bevacizumab arm. QOL and exploratory biomarkers studies will be also presented at time of the meeting. **Conclusion:** Bevacizumab addition to pemetrexed/cis-platin provides a significantly longer survival in pts with MPM, with acceptable toxicity, making this triplet a new treatment paradigm. **Keywords:** IFCT, Mesothelioma, bevacizumab, phase III

QUALITY OF LIFE AND TRIALS
MONDAY, SEPTEMBER 7, 2015 - 10:45-12:15

ORAL12.05 Impact of Time to Drug Approval on Potential Years of Life Lost: The Compelling Need for Improved Trial and Regulatory Efficiency David J. Stewart[1], Andrew A. Stewart[2], Paul Wheatley-Price[1], Gerald Batist[3], Hagop Kantarjian[4], Joan Schiller[5], Mark Clemons[1], John-Peter Bradford[6], Laurel Gibbons[7], Razelle Kurzrock[8] [1]*Medicine, University of Ottawa, Ottawa/ON/Canada,* [2]*The Lethal Diseases Help Project, Ottawa/ON/Canada,* [3]*Mcgill University, Montreal/QC/Canada,* [4]*University of Texas MD Anderson Cancer Center, Houston/TX/United States of America,* [5]*Hematology/Oncology, UT Southwestern, Dallas/United States of America,* [6]*Bradford Bachinski Ltd and the Lethal Diseases Help Project, Ottawa/ON/Canada,* [7]*The Ottawa Hospital and the Lethal Diseases Help Project, Ottawa/AB/Canada,* [8]*University of California San Diego, San Diego/CA/United States of America*

Background: Survival of incurable cancer patients is improving gradually. Several hundred new therapies are under development. However, internationally, regulatory complexity slows progress by increasing drug development costs (hence, fewer drugs can be assessed with available resources) and by producing numerous speed bumps that delay approval of useful drugs and that increase resources required to document that other agents are ineffective. **Methods:** We assessed cancer therapies undergoing phase III trials between 2001 and 2015. To be included, trials had to document statistically significant improvement in overall survival. We excluded adjuvant trials and trials in uncommon malignancies. To determine the number of life-years potentially lost per year required for drug approval, we multiplied the improvement in median survival in years by the estimated number of patients (North American and worldwide) dying annually from the relevant malignancy. **Results:** In the Table, we present the life-years lost per year required for approval for 21 therapies in 10 malignancies. When the combined impact of all tumor sites and drugs are considered together, there were 29 life-years lost in North America per hour of delay in therapy approval (1 for every 2 minutes of delay) and 260 life-years lost worldwide per hour of delay (1 for every 14 seconds of delay). These numbers do not take into account impact of drugs non-evaluable due to cross-over or missing survival data, drugs that were prematurely abandoned, drugs still undergoing investigation, or approaches for non-malignant lethal diseases.

Malignancy	Therapy	Median survival gain (yrs)	Life-years lost per year required to achieve drug approval*	
			North America	Worldwide
NSCLC	Erlotinib	0.17	25,344	198,730
NSCLC	Bevacizumab	0.17	25,344	198,730
NSCLC (EGFR-expressing)	Cetuximab	0.10	12,899	101,150
NSCLC (squamous)	Nivolumab	0.27	11,917	93,450
Breast	Eribulin	0.21	9,536	95,485
Breast (HER2+ve)	Trastuzumab	0.40	2,743	27,504
Breast (HER2+ve)	Trastuzumab emtansine	0.48	3,312	33,211
Breast (HER2+ve)	Pertuzumab	1.31	8,969	89,938
Colorectal	Bevacizumab	0.39	23,139	238,610
Colorectal	Oxaliplatin	0.38	22,136	228,263
Colorectal	Regorafinib	0.12	6,906	71,218
Colorectal (EGFR-expressing)	Cetuximab	0.13	7,157	73,805
Gastric (HER2+ve)	Trastuzumab	0.23	605	34,871
Head/Neck	Cetuximab	0.23	1,988	25,920
Prostate	Cabazitaxel	0.20	6,308	51,680
Prostate	Enzalutamide	0.40	12,616	103,360
Prostate	Abiraterone	0.38	12,080	98,967
Prostate	Sipuleucel-T	0.36	11,354	93,024
Renal	Temsirolimus	0.30	4,757	34,800
Renal	Sunitinib	0.38	6,026	44,080
Renal**	Sorafenib	0.29	4,599	33,640
Melanoma	Ipilumumab	0.31	3,382	8,938
Melanoma (BRAF-mutant)	Vemurafenib	0.33	1,785	8,938
Melanoma (BRAF-wildtype)	Nivolumab	0.42	2,284	11,440
Myeloma	Pomalidomide	0.39	4,923	28,860
Myeloma	Bortezomib	1.11	13,985	81,992
Hepatocellular	Sorafenib	0.23	5,290	160,057
Cumulative (all sites)			251,626	2,278,662

* Median survival gain (years) x no. patients dying per year
**Placebo patients censored at time of cross-over

Conclusion: Clearly, the survival gains associated with the foregoing drugs are only modest. Despite this, there would be a large negative impact associated with approval delays even if factors such as co-morbidities, performance status, ability to pay, etc, limit the number of patients treated to a fraction of the total dying from a specific malignancy. There are numerous opportunities to improve efficiency of cancer drug approval without sacrificing safety or data integrity. This requires urgent attention. **Keywords:** regulatory delays, Life-years lost, urgent need for reform

MASCC-IASLC JOINT SESSION: PALLIATIVE AND SUPPORTIVE CARE
TUESDAY, SEPTEMBER 8, 2015 - 16:45-18:15

ORAL29.01 Results From Phase III Trials of Anamorelin in Advanced Non-Small Cell Lung Cancer Patients with Cachexia: ROMANA 1 and 2 Amy Abernethy[1], Kenneth Fearon[2], John Friend[3], Ying Yan[3], Elizabeth Duus[3], David Currow[4] [1]*Durham University, Durham/NC/United States of America,* [2]*Western General Hospital, Edinburgh/United Kingdom,* [3]*Helsinn Therapeutics (Us), Inc., Iselin/NJ/United States of America,* [4]*Flinders University, Adelaide/SA/Australia*

Background: Cachexia is a debilitating condition often observed in patients with advanced non-small cell lung cancer (NSCLC). A decrease in body weight (BW), in particular loss of lean body mass (LBM), is a primary characteristic, and is associated with worsening functional status, quality of life, and survival. Despite the high prevalence and substantial clinical impact of cachexia in patients with advanced cancer, limited therapeutic options exist. Anamorelin is a novel, orally active, selective ghrelin receptor agonist that mimics the appetite-enhancing and anabolic effects of ghrelin. ROMANA 1 and 2 are two randomized, double-blind, Phase III trials evaluating the efficacy and safety of anamorelin in patients with advanced NSCLC and cachexia. **Methods:** In ROMANA 1 (NCT01387269; N=484) and ROMANA 2 (NCT01387282; N=495), patients with unresectable stage III/IV NSCLC and cachexia (≥5% weight loss during prior 6 months or body mass index <20kg/m^2) were randomized (2:1) to anamorelin 100 mg daily or placebo, for 12 weeks. Co-primary endpoints were change in LBM and handgrip strength (HGS) over 12 weeks. Secondary endpoints included change in BW and in the anorexia/cachexia domain of the Functional Assessment of Anorexia/Cachexia Therapy questionnaire over 12 weeks, and pooled 1-year overall survival (OS) from both studies. Exploratory endpoints included summarizing the incidence of patients who maintained/gained LBM from baseline during 12 weeks by treatment group. Post-hoc analysis compared OS data in patients who had decrease in LBM during 12 weeks versus those who maintained/gained LBM. Safety and tolerability of anamorelin were also evaluated. **Results:** Over 12 weeks, anamorelin significantly increased median LBM versus placebo in ROMANA 1 (1.10 vs –0.44 kg; p<0.001) and ROMANA 2 (0.75 vs –0.96 kg; p<0.001); in both studies there was no difference in HGS changes between treatment arms. A significantly greater proportion of patients in the anamorelin arm versus the placebo arm maintained/gained LBM in both ROMANA 1 (58.1% vs 36.9%; p<0.001) and ROMANA 2 (51.5% vs 26.5%; p<0.001). Post-hoc analysis showed that OS was improved for patients who maintained/gained LBM versus patients who lost LBM (HR, 0.53 [95% CI, 0.42, 0.68]; p<0.001). Anamorelin-treated patients also significantly gained BW (2.20 vs 0.14 kg; p<0.001, and 0.95 vs –0.57 kg; p<0.001), and had significantly improved anorexia-cachexia symptoms and concerns (4.12 vs 1.92; <0.001, and 3.48 vs 1.34; p=0.002), compared with placebo-treated patients, in ROMANA 1 and 2, respectively.

The most frequent drug-related adverse event (AE) in the anamorelin arm in both ROMANA 1 and 2 was hyperglycemia (5.3% and 4.2%); there were few drug-related grade ≥3 AEs in the anamorelin arm versus the placebo arm (0.9% vs 1.2% and 2.7% vs 2.5%). **Conclusion:** Anamorelin significantly increased LBM and BW, and improved anorexia-cachexia symptoms and concerns, compared with placebo, in patients with advanced NSCLC and cachexia. Change from baseline in HGS was similar in both treatment arms. A significantly greater proportion of patients maintained/gained LBM in the anamorelin arm versus the placebo arm. When LBM was stable or increased, OS was significantly improved. Anamorelin treatment over 12 weeks was also well tolerated.
Keywords: Cachexia, Anamorelin, ROMANA, Lean body mass

LATE PUBLICATION ABSTRACTS TUESDAY, SEPTEMBER 8, 2015

MOVING BEYOND A SMOKING RELATED-CANCER TO THE YOUNG, NEVER-SMOKERS AND INHERITED DISEASE
TUESDAY, SEPTEMBER 8, 2015 - 10:45-12:15

ORAL22.01 Increasing Incidence of Never Smokers in Non Small Cell Lung Cancer (NSCLC) Patients Lorraine Pelosof[1], Chul Ahn[2], Leora Horn[3], Alejandra Madrigales[1], Joan Cox[4], Judith N. Roberts[5], John Minna[1], Joan Schiller[1] [1]*Hematology/Oncology, UT Southwestern, Dallas/TX/United States of America,* [2]*Biostatistics, UT Southwestern, Dallas/TX/United States of America,* [3]*Vanderbilt-Ingram Cancer Center, Nashville/TN/United States of America,* [4]*Parkland Hospital, Dallas/United States of America,* [5]*Vanderbilt-Ingram Cancer Center, Nashville/United States of America*

Background: It is estimated that 10-15% of lung cancer cases occur in never smokers. The cause of lung cancer in these patients includes many possible environmental factors but the precise cause in a given case is often uncertain. Additionally, there has been significant debate about whether the rate of lung cancer in these never smokers is increasing. Using our institutions' cancer registry data, our objective was to determine if the proportion of never smokers with lung cancer is increasing. **Methods:** We conducted a retrospective study using lung cancer registry data from The University of Texas Southwestern Medical Center in Dallas, Parkland Hospital in Dallas, and Vanderbilt University in Nashville. These registries were queried between 1990 and 2013 for demographic information including gender, age at diagnosis, diagnosis [non small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)], and self-reported smoking history. A total of 10,568 NSCLC cases and 1504 SCLC cases were analyzed. Logistic regression analysis was performed to assess the incidence of never smokers with lung cancer. **Results:** The percentage of never smokers increased among NSCLC pts between 1990 and 2013 [Table 1]. Univariate logistic regression demonstrated an increasing proportion of never smokers among NSCLC cases ($p < 0.0001$ for year) and multivariate logistic regression also demonstrates this increase ($p < 0.0001$ for year) after controlling for age and gender. Never smokers with NSCLC were more likely to be female (65.3%, $p < 0.0001$) than males. The increase in the percentage of NSCLC never smokers was seen at both university hospitals and the Dallas county hospital. In contrast, the percentage of never smokers among SCLC cases did not significantly increase during this time period.

Table 1: Percentage of never smokers

	UTSW		Parkland		Vanderbilt	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1990-1995	8.9	1.7	-	-	-	-
1996-2000	9.4	1.4	8.4	2.8	9.8	2.2
2001-2005	9.9	0	7.8	2.9	10.4	2.3
2006-2010	13.8	7.0	13.1	2.9	10.6	2.2
2011-2013	19.5	4.5	13.9	1.3	12.9	2.3
p value	<.0001	0.11	0.0001	0.59	0.02	0.97
overall NSCLC p value	<.0001					
overall SCLC p value	0.4204					

Conclusion: This multi-institution study demonstrates an increasing proportion of never smokers with NSCLC between 1990 and 2013 in a large, geographically and demographically diverse population. Because the biology and, thus, often the treatment options of lung cancer in never smokers differs from that of smokers, further investigation is warranted as to the etiology of the increasing incidence of never-smoker lung cancer. **Keywords:** never smoker, NSCLC

MOVING BEYOND A SMOKING RELATED-CANCER TO THE YOUNG, NEVER-SMOKERS AND INHERITED DISEASE
TUESDAY, SEPTEMBER 8, 2015 - 10:45-12:15

ORAL22.05 The Genomics of Young Lung Cancer Study Barbara J. Gitlitz[1], Deborah Morosini[2], Alicia Sable-Hunt[3], Bonnie J Addario[3], Mark B. Jennings[1], Silvia Novello[4], Tiziana Vavala[4], Stacy Mach[5], Carol Jones[6], Geoffrey R. Oxnard[5] [1]*University of Southern California Keck School of Medicine, Los Angeles/CA/United States of America,* [2]*Foundation Medicine, Boston/MA/United States of America,* [3]*Addario Lung Cancer Medical Institute, San Carlos/CA/United States of America,* [4]*University of Turin, Turin/Italy,* [5]*Dana-Farber Cancer, Boston/MA/United States of America,* [6]*University of Southern California Keck School of Medicine, Los Angeles/United States of America*

Background: Primary lung cancer is increasingly understood as a heterogeneous disease made up of genomically defined subtypes requiring distinct treatment strategies. We hypothesize young age at diagnosis (< 40 years) is a clinical characteristic associated with an increased chance for a targetable genomic alteration. Our ALCMI study prospectively characterizes the somatic and germline genomics of young lung cancer (GYLC). Our goals are to identify a genomically enriched subtype of lung cancer, facilitate delivery of targeted therapy and lay groundwork for further studies of heritable and environmental lung cancer risk factors. **Methods:** Accrual opened July 2014. Patients are eligible if they were diagnosed with bronchogenic lung cancer less than age 40. A study website allows for virtual consenting so patients can participate remotely from anywhere in the world; and use social media to share our trial. We have an integrated data and bio repository that allows for seamless communication and completion of study activities like remote consenting and routing of blood and tumor specimens. We have defined 7 genomic alterations of interest based on the Lung Cancer Mutational Consortium (LCMC) (EGFR, KRAS, HER2, BRAF, ALK, ROS1, RET). We aim to demonstrate that the prevalence of targetable genomic alterations will be greater in our population compared to the LCMC and have powered our study to show an increase from 35% to 50%; and an improvement in use of targeted therapy from 22% to 40%. On study subjects without a known genotype will undergo comprehensive genomic profiling with the FoundationOne test to ensure that all of these genes have been tested. Subjects with advanced adenocarcinoma who are wild type for all 7 genes will receive additional genomic profiling using the FoundationOne Heme test; with the goal of identifying novel oncogenic drivers. Additional investigational genomics will include blood for germline analysis and plasma genomics. All on study genomic analysis is at no cost to the participant. **Results:** Preliminary results of the first 33 subjects show: Average age at diagnosis: 33 years; Range 22-39; Histology: adenocarcinoma n=29, squamous cell n=4; Stage at diagnosis: stage 4 n=26 (79%) stages 1-3 n=7 (21%). Of those with stage 4 adenocarcinoma (n=24); 18:24 (75%) have either an ALK re arrangement n=10 (42%), an EGFR activating mutation n=5 (21%) or a ROS1 fusion n=3 (13%). **Conclusion:** The trial is currently accruing (NCT02273336) https://www.openmednet.org/site/alcmi-goyl. We have accrued patients from the USA, Europe and Australia. Thus far in our prospective series those diagnosed with primary NSCLC < age 40 tend to have stage 4 adenocarcinoma. Preliminary results exceed our statistical expectation with 75% of our metastatic adenocarcinoma patients having an actionable mutation. We plan on presenting data for the first time at WCLC-2015 on the first 50 subjects. (Study, supported by grants from BJALCF, Beth Longwell Foundation, Peter Barker Foundation, Genentech, Schmidt Legacy Foundation, and Upstage Lung Cancer) **Keywords:** Young Lung Cancer, Virtual Consenting, enriched population, Genomics

MOVING BEYOND A SMOKING RELATED-CANCER TO THE YOUNG, NEVER-SMOKERS AND INHERITED DISEASE
TUESDAY, SEPTEMBER 8, 2015 - 10:45-12:15

ORAL22.07 Oncogenic Profiling in Lung Adenocarcinoma Emerged in the Youth Kosuke Tanaka, Yuko Oya, Tatsuya Yoshida, Junichi Shimizu, Yoshitsugu Horio, Toyoaki Hida, Yasushi Yatabe *Aichi Cancer Center, Nagoya/Japan*

Background: *EGFR, Kras* mutations and *EML4-ALK* translocations were frequently positive in adenocarcinoma among lung cancer, and in fewer cases *HER2, BRAF* mutations or *RET, ROS1* translocations were identified. Although adenocarcinomas emerged in the youth are estimatedly associated with some driver oncogenes including these mutations/translocations, the detail remains unknown. **Methods:** We retrospectively screened 55 consecutive patients who were diagnosed as stage I-IV adenocarcinoma at the age of 40 years or less in 2009-2014. We analyzed clinical and genetic characteristics among them. **Results:** Out of 55 patients, 21 (38%) were male, 24 (44%) were never-smoker, and 38 (69%) were stage IV, with the median age of 36 years (range; 26-40). Forty-five patients (82%) were identified some driver oncogene. 26 (47%) had *EML4-ALK* translocation, 13 (24%) had *EGFR* mutation, and 2 (4%) had *Kras* mutation. We examined rare oncogenes in 10 out of 14 triple-negative patients, which revealed three patients had *HER2* mutation and two had *RET* translocation. **Conclusion:** 82% of adenocarcinomas emerged in the youth were identified some targetable driver oncogenes. Not only *EGFR* mutation or *EML4-ALK* translocation, rare oncogene examination is necessary especially among these populations. **Keywords:** oncogene, Adenocarcinoma, youth

CT DETECTED NODULES - PREDICTING BIOLOGICAL OUTCOME
TUESDAY, SEPTEMBER 8, 2015 - 10:45-12:15

ORAL24.03 Increasing Incidence of Non-Smoking Lung Cancer: Presentation of Patients with Early Disease to a Tertiary Institution in the UK Maria Elena Cufari[1], Chiara Proli[1], Manraj Phull[1], Hilgardt Raubenheimer[1], May Al Sahaf[2], Nizar Asadi[2], Periklis Perikleous[2], Anna Allan[2], Lynn Shedden[1], Hemangi Chavan[1], Zakiyah Niwaz[3], Andre Kubler[1], Andrew G. Nicholson[4], Patrizia Viola[5], Vladimir Anikin[2], Emma Beddow[2], Niall Mcgonigle[2], Michael Dusmet[1], Simon Jordan[1], George Ladas[1], Eric Lim[1] [1]*Department of Thoracic Surgery, Royal Brompton and Harefield NHS Trust, London/United Kingdom,* [2]*Thoracic Surgery, Royal Brompton and Harefield NHS Trust, London/United Kingdom,* [3]*Clinical Outcomes Analyst - Lung Division, Royal Brompton and Harefield NHS Trust, London/United Kingdom,* [4]*Department of Histopathology, Royal Brompton and Harefield NHS Trust, London/United Kingdom,* [5]*Histopathology, Royal Brompton Hospital, London/United Kingdom*

Background: Lung cancer in never-smokers is recognised as a distinct entity. Many are expected to present late. As there are no established aetiological factors, identification of patients at risk is challenging. The aim of the study is to define the incidence and

clinical features of never-smokers presenting sufficiently early for surgery to determine if it is possible to identify patients at risk. **Methods:** We retrospectively analysed data from a prospectively collected database of patients who underwent surgery at our institution. The incidence was defined as number of never-smokers versus current and ex-smokers by year. Clinical features at presentation were obtained and collated as frequency (percentage). **Results:** A total of 2170 patients underwent surgical resection for lung cancer from March 2008 to November 2014. The annual incidence of developing lung cancer in never-smokers increased from 13, 15, 18, 19, 20, 20 to 28 percent respectively, attributable to an absolute increase in number and not a change in the ratio of never smokers to current and ex-smokers. A total of 436 (20%) patients were never smokers. The mean age at presentation was 60 (16 SD) years and 295 (67%) were female. Good lung function was observed with mean predicted FEV1 of 90% (23 SD) and FVC of 97% (25 SD). The majority histological types were adenocarcinoma 54% and carcinoid 27%. The main presenting features were non-specific consisting of cough in 142 (34%), chest infections in 75 (18%) and haemoptysis in 46 (11%). Recurrent chest infections were predominantly a symptom of central carcinoid tumours (30 versus 15 percent; P=0.004). A total of 59 (14%) were detected on incidental chest film, 127 (30%) on incidental CT, 32 (7%) on incidental PET/CT and 4(1%) on incidental MRI. **Conclusion:** We observed more than double the annual incidence of never smokers presenting with non small cell lung cancer, in the last 7 years, increasing from 13 to 28 percent, and hypothesise that this is representative of the UK, as we are one of the highest surgical volume centres in our country. Patients present with non-specific symptoms and the majority were detected on incidental imaging. We conclude that imaging is likely to play a more important role and further efforts need to be expended on early detection of lung cancer in this increasing cohort without any observable risk factors.
Keywords: never-smokers, non small cell lung cancer, early disease

T CELL THERAPY FOR LUNG CANCER
TUESDAY, SEPTEMBER 8, 2015 - 16:45-18:15

ORAL28.03 Genetic-Engineering Strategies to Enhance CAR T-Cell Therapy Efficacy against PD-L1 Expressing Lung Adenocarcinoma and Mesothelioma

Leonid Cherkassky[1], Aurore Morello[1], Jonathan Villena-Vargas[1], Marissa Mayor[1], David R. Jones[1], Michel Sadelain[2], Prasad S. Adusumilli[1] [1]*Thoracic Surgery, Memorial Sloan-Kettering Cancer Center, New York/United States of America,* [2]*Center for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York/United States of America*

Background: Our laboratory has published (*Sci Transl Med* 2014) on the anti-tumor efficacy of mesothelin (MSLN)-targeted chimeric antigen receptor (CAR) transduced T cells. The purpose of this study is to investigate the efficacy of CAR T cells in a predominantly immunosuppressive environment in against lung adenocarcinoma (LAC) and malignant pleural mesothelioma (MPM) overexpressing PD-L1. We *hypothesized* that CAR T-cell efficacy can be inhibited by PD-L1 overexpression, which can be overcome by genetic engineering combining optimal costimulation and coinhibitory blockade to potentiate CAR T-cell efficacy. **Methods:** Human T cells were transduced with a CAR specific for MSLN and possessing CD3zeta domain alone (Mz) or CD3zeta domain and CD28 costimulation domain (M28z). To counteract PD1/PD-L1, M28z T cells were also costranduced with PD1 targeting shRNAs or with PD1 dominant negative receptor (PD1-DNR), which contains the extracellular binding region of PD1 but lacks the intracellular signaling domain. T-cell efficacy (proliferation, cytokine secretion, cytotoxicity) was evaluated *in vitro* upon antigen repeated stimulation on PD-L1 expressing cell lines and in clinically-relevant MPM and LAC mouse models developed in the lab. A single low dose of CAR T cells were adoptively transferred intrapleurally or intravenously and anti-tumor efficacy was assessed by median survival and by tumor burden progression using bioluminescent imaging. **Results:** Compared to Mz T cells, M28z T cells bearing the CD28 costimulation domain exhibit an enhanced cytotoxicity, Th1 cytokine secretion and proliferation even in the presence of PD-L1 expressing cells. *In vivo*, M28z T cells exhibit higher persistence and prolong median survival compared to Mz (64 vs 29 days, $p<0.05$). However, when treated with a lower dose (E:T 1:12,000) of M28z T cells, treated mice died from tumor relapse; tumor harvest analysis demonstrated upregulation of PD1 and PD-L1 on T cells and tumor cells, respectively. Further analysis demonstrated that antigen-activated CAR T-cell secreted effector cytokines induced PD-L1 expression on cancer cells. We then confirmed *in vitro* that PD-L1/PD1 pathway promotes M28z T cells exhaustion by inhibiting cytotoxicity and cytokine secretion. M28z CAR T cells coexpressing shRNAs targeting PD1 or PD1-DNR lacking the intracellular signaling domain retained T cell effector function against PD-L1 expressing cancer cells. *In vivo,* mice treated with a low dose M28z PD1-DNR (E:T 1:12,000) had significantly enhanced tumor burden control and prolonged median survival (M28z vs M28z PD1-DNR, 56 vs 82 days, $p=0.001$). **Conclusion:** Our results demonstrate the benefit of optimal signaling in CAR T cells by simultaneously providing costimulation and coinhibitory blockade to counteract PD-L1/PD1, a major mechanism of immunosuppression. This genetic-engineering strategy is immediately translatable for clinical trials to enhance the efficacy of CAR T cell therapy, and is specific for MPM and LAC patient tumor microenvironment.
Keywords: CAR T cells, PD-L1, Immunotherapy, immunosuppression

LATE PUBLICATION ABSTRACTS WEDNESDAY, SEPTEMBER 9, 2015

PRESIDENTIAL SYMPOSIUM INCLUDING TOP 4 ABSTRACTS
WEDNESDAY, SEPTEMBER 9, 2015 - 10:45-12:15

PLEN04.01 A Randomized, Phase III Study Comparing Carboplatin/Paclitaxel or Carboplatin/Paclitaxel/Bevacizumab with or without Concurrent Cetuximab in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC): SWOG S0819

Roy Herbst[1], Mary Redman[2], Edward S. Kim[3], Thomas J. Semrad[4], Lyudmila Bazhenova[5], Gregory Masters[6], Kurt Oettel[7], Perry Guaglianone[8], Christopher Reynolds[9], Anand Karnad[10], Susanne M. Arnold[11], Marileila Varella-Garcia[12], James Moon[2], Philip C. Mack[13], Charles D. Blanke[14], Fred R. Hirsch[12], David R. Gandara[4] [1]*Medical Oncology, Yale Cancer Center, New Haven, CT/United States of America,* [2]*Swog Statistical Center, Portland/OR/United States of America,* [3]*Levine Cancer Institute, Carolinas Healthcare System, Charlotte/NC/United States of America,* [4]*University of California at Davis, Sacramento/CA/United States of America,* [5]*Moores Cancer Center, University of California San Diego, La Jolla/United States of America,* [6]*Helen F. Graham Cancer Center & Research Institute, Wilmington/DE/United States of America,* [7]*Gundersen Lutheran CCOP/Gundersen Health System, Lacrosse/WI/United States of America,* [8]*Heartland Cancer Research NCORP/Cancer Care Specialists of Central Illinois, Decatur/IL/United States of America,* [9]*Michigan Cancer Research Consortium NCORP/St. Joseph Mercy Health System, Ann Arbor/MN/United States of America,* [10]*University of Texas Health Science Center at San Antonio, Santo Antonio/TX/United States of America,* [11]*Medical Oncology, University of Kentucky, Lexington/KY/United States of America,*[12]*Medicine, University of Colorado School of Medicine, Aurora/United States of America,* [13]*UC Davis Comprehensive Cancer Center, Sacramento/CA/United States of America,* [14]*Swog Group Chair's Office/Oregon Health & Science University, Portland/OR/United States of America*

Background: Cetuximab, a chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR), moderately increases survival in patients with advanced NSCLC. Our prior work suggested that EGFR gene copy number measured by fluorescent in-suit hybridization (FISH) could identify those patients most likely to benefit. **Methods**: Patients eligible for this NCTN multicenter open-label, phase III trial had histologically or cytological confirmed Stage IV NSCLC that was newly diagnosed or recurrent after previous surgery or radiation. Patients with controlled brain metastases were allowed entry. All patients were required to have tumor tissue available for EGFR FISH testing. Randomization was stratified by appropriateness for bevacizumab treatment, smoking status and M-substage. The co-primary objectives were progression-free survival (PFS) in EGFR-FISH positive (FISH+) patients and overall survival (OS) in the overall study population (OSP). Secondary objectives were OS in FISH-positive patients and clinical outcomes (PFS and OS) comparison among bevacizumab-appropriate (BA) and inappropriate (BI) patients. **Results:** The final accrual was 1,333 total and 1,313 eligible patients (control arm: 657 total, 275/382 BA/BI; cetuximab-containing arm: 656 total, 279/377 BA/BI). EGFR FISH status was determined on 976 patients, with 400 (41%) FISH+. Squamous carcinoma (SCCA) represented 24-25% of patients. PFS and OS were not significantly different in the OSP (HR (95%CI) =0.98 (0.87-1.09) and 0.94(0.84-1.06), respectively). There is some indication of benefit in PFS and OS (HR 0.91 (0.74-1.12) and 0.83 (0.67-1.04), respectively) in FISH+ patients, albeit not statistically significant. However, among FISH+ BI and SCCA patients, effect estimates for OS were 0.75 (0.57-1.00) and 0.56 (0.37-0.84), respectively. Cetuximab was generally well tolerated with a spectrum of adverse events consistent with prior reports **Conclusion**: The addition of cetuximab had minimal effect in unselected advanced NSCLC patients. In FISH+ patients there is a suggestion of benefit, predominantly in SCCA and BI. These data support using a new marker for determining who should receive an EGFR antibody inhibitor with chemotherapy. **Support:** NIH/NCI/NCTN grants SWOG: CA180888, CA180819; ECOG/ACRIN: CA180820; Alliance: CA180821; and in part by Bristol-Myers Squibb Co.

	N		PFS		OS	
Analysis Group	**OSP**	**FISH+**	**OSP**	**FISH+**	**OSP**	**FISH+**
All Patients						
Cetuximab-Containing Arm, Median, 95% CI	656	199	4.6(4.2-5.2)	5.4(4.5-5.7)	10.9(9.6-12.0)	13.4(11.7-14.8)
Control Arm, Median, 95% CI	657	201	4.5(4.2-4.9)	4.8(3.9-5.5)	9.4(8.7-10.3)	9.8(8.7-12.1)
Hazard Ratio, 95% CI			0.98(0.87-1.09)	0.91(0.74-1.12)	0.94(0.84-1.06)	0.83(0.67-1.04)
2-sided p-value			0.68	0.37	0.34	0.10
BA						
Cetuximab-Containing Arm, Median, 95% CI	279	86	5.6(5.3-6.1)	6.2(5.7-7.4)	12.7(10.9-13.4)	15.5(13.4-18.4)
Control Arm, Median, 95% CI	275	80	5.9(5.5-6.6)	6.7(5.7-8.0)	11.6(10.5-13.8)	13.2(11.2-19.1)
Hazard Ratio, 95% CI			1.05(0.88-1.25)	1.07(0.77-1.47)	1.04(0.86-1.25)	0.97(0.69-1.38)
2-sided p-value			0.57	0.70	0.70	0.88
BI						
Cetuximab-Containing Arm, Median, 95% CI	377	113	4.1(3.6-4.4)	4.5(3.8-5.2)	9.2(8.2-10.9)	11.2(8.6-12.9)
Control Arm, Median, 95% CI	382	121	3.8(3.1-4.2)	3.7(2.8-4.6)	8.2(7.3-8.7)	8.7(5.9-9.7)
Hazard Ratio, 95% CI			0.93(0.80-1.07)	0.82(0.63-1.07)	0.88(0.76-1.03)	0.75(0.57-1.00)
2-sided p-value			0.31	0.14	0.12	0.05
SCCA						
Cetuximab-Containing Arm, Median, 95% CI	160	55	4.2(3.7-4.6)	4.5(3.8-5.2)	9.6(8.2-11.5)	11.8(8.6-13.5)
Control Arm, Median, 95% CI	161	56	3.7(2.8-4.3)	2.8(2.6-4.1)	8.0(7.1-8.9)	6.4(4.2-8.7)
Hazard Ratio, 95% CI			0.88(0.70-1.11)	0.68(0.46-1.01)	0.85(0.67-1.08)	0.56(0.37-0.84)
2-sided p-value			0.29	0.06	0.18	0.006

PRESIDENTIAL SYMPOSIUM INCLUDING TOP 4 ABSTRACTS
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PLEN04.03 Randomized Phase III Trial of Adjuvant Chemotherapy with or without Bevacizumab in Resected Non-Small Cell Lung Cancer (NSCLC): Results of E1505 Heather A. Wakelee[1], Suzanne E. Dahlberg[2], Steven M. Keller[3], William J. Tester[4], David R. Gandara[5], Stephen L. Graziano[6], Alex Adjei[7], Natasha Leighl[8], Seena C. Aisner[9], Jan M. Rothman[10], Jyoti Patel[11], Mark D. Sborov[12], Sean R. Mcdermott[13], Roman Perez-Soler[14], Anne M. Traynor[15], Charles Butts[16], Tracey Evans[17], Leora Horn[18], Suresh S. Ramalingam[19], Joan Schiller[20] [1]*Medicine (Oncology), Stanford Cancer Intitute/Stanford University, Stanford/CA/United States of America,* [2]*Dana Farber Cancer Institute/Harvard University, Boston/MA/United States of America,* [3]*Cardiovascular and Thoracic Surgery, Montefiore Medical Center, Bronx/NY/United States of America,* [4]*Albert Einstein Medical Center, Philadelphia/PA/United States of America,* [5]*Uc Davis Comprehensive Cancer Center, Sacramento/United States of America,* [6]*Medical Oncology, Suny Upstate Medical University, Syracuse/NY/United States of America,* [7]*Medicine, Roswell Park Cancer Institute, Buffalo/NY/United States of America,* [8]*Princess Margaret Cancer Centre, Toronto/ON/Canada,* [9]*Rutgers New Jersey Medical School, Newark/NJ/United States of America,* [10]*The Regional Cancer Center, Erie/PA/United States of America,* [11]*Northwestern University, Chicago/IL/United States of America,* [12]*Edina Clinic, Edina/United States of America,* [13]*Medical Oncology, The Adelaide and Meath Hospital, Dublin, Dublin/Ireland,* [14]*Oncology, Montefiore Medical Center, Bronx/NY/United States of America,* [15]*University of Wisconsin, Madison/WI/United States of America,* [16]*Division of Oncology, Univeristy of Alberta, Edmonton/AB/Canada,* [17]*University of Pennsylvania, Philadelphia/PA/United States of America,* [18]*Vanderbilt University Medical Center, Nashville/TN/United States of America,* [19]*Winship Cancer Institute, Emory University, Atlanta/GA/United States of America,* [20]*Hematology/Oncology, UT Southwestern, Dallas/United States of America*

Background: Adjuvant chemotherapy for resected early stage NSCLC provides modest survival benefit. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, improves outcomes when added to platinum-based chemotherapy in advanced stage non-squamous NSCLC. We conducted a phase 3 study to evaluate the addition of bevacizumab to adjuvant chemotherapy in early stage resected NSCLC. The primary endpoint was overall survival and secondary endpoints included disease-free survival and toxicity assessment. **Methods:** Patients with resected stage IB (≥4 centimeters) to IIIA (AJCC 6th edition) NSCLC were enrolled within 6-12 weeks of surgery and stratified by chemotherapy regimen, stage, histology and sex. All patients were to receive adjuvant chemotherapy consisting of a planned 4 cycles of every 3 week cisplatin at 75 mg/m^2 with either vinorelbine, docetaxel, gemcitabine or pemetrexed. Patients were randomized 1:1 to arm A (chemotherapy alone) or arm B, adding bevacizumab at 15 mg/kg every 3 weeks starting with cycle 1 of chemotherapy and continuing for 1 year. Post-operative radiation therapy was not allowed. The study had 85% power to detect a 21% reduction in the overall survival (OS) hazard rate with a one-sided 0.025-level test. **Results:** From July 2007 to September 2013, 1501 patients were enrolled. Patients were 49.8% male, predominantly white (87.9%) with a median age of 61 years. Patients enrolled had tumors that were 26.2% stage IB, 43.8% stage II and 30.0% stage IIIA and 28.2% of patients had squamous cell histology. Chemotherapy options were utilized with the following distribution: vinorelbine 25.0%, docetaxel 22.9%, gemcitabine 18.9% and pemetrexed 33.2%. At a planned interim analysis, with 412 of 676 overall survival events needed for full information (60.9%), though the pre-planned futility boundary was not crossed, the Data Safety Monitoring Committee recommended releasing the trial results based on the conditional power of the logrank test. At the time of interim analysis, with a median follow-up time of 41 months, the OS hazard ratio comparing the bevacizumab containing arm (Arm B) to chemotherapy alone (Arm A) was 0.99 (95% CI: 0.81-1.21, p=0.93). The DFS hazard ratio was 0.98 (95% CI: 0.84-1.14, p=0.75). Completion of treatment per protocol was 80% on Arm A and 36% on Arm B. Statistically significantly increased grade 3-5 toxicities of note (all attributions) included: overall worst grade (67% versus 84%); hypertension (8% versus 30%), and neutropenia (33% versus 38%) on Arms A and B, respectively. There was no significant difference in grade 5 adverse events per arm with 16 (2%) on arm A and 19 (3%) on arm B. **Conclusion:** The addition of bevacizumab to adjuvant chemotherapy failed to improve survival for patients with surgically resected early stage NSCLC. **Keywords:** adjuvant chemotherapy, bevacizumab, early stage NSCLC

PRESIDENTIAL SYMPOSIUM INCLUDING TOP 4 ABSTRACTS
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PLEN04.05 Multiregion Whole Exome and Transcriptome Sequencing Defines the Genomic Spectrum of EGFR+ NSCLC and Reveals Novel Mechanisms of TKI Resistance Daniel S.-W. Tan[1], Rahul Nahar[2], Angela Takano[3], Alexis Khng[2], Tong Zhang[2], Tina Puay-Theng Koh[4], Apoorva Gogna[5], Tony Kiat-Hon Lim[3], Win Aung Zaw[6], Xingliang Liu[2], Audrey Teo[2], Cheryl Chan[2], Yin Yeng Lee[2], Gopal Iyer[7], Liang He Chen[8], Mei-Kim Ang[1], Quan-Sing Ng[1], Chee-Keong Toh[1], Ravindran Kanesvaran[1], Amit Jain[1], Anantham Devanand[9], Vidhya Krishnan[2], Pauline Ng[2], Bien Soo Tan[5], Chong Hee Lim[10], Balram Chowbay[11], Wan-Teck Lim[1], Wai Leong Tam[2], Bing Lim[2], Eng Huat Tan[1], Wei Wei Zhai[2], Axel Hillmer[2] [1]*Department of Medical Oncology, National Cancer Center Singapore, Singapore/Singapore,* [2]*Genome Institute of Singapore, Singapore/Singapore,* [3]*Department of Pathology, Singapore General Hospital, Singapore/Singapore,* [4]*Division of Surgical Oncology, National Cancer Center Singapore, Singapore/Singapore,* [5]*Department of Diagnostic Radiology, Singapore General Hospital, Singapore/Singapore,* [6]*Clinical Trial Office, National Cancer Center Singapore, Singapore/Singapore,* [7]*Cancer Therapeutics Research Laboratory, National Cancer Center Singapore, Singapore/Singapore,* [8]*Cancer Stem Cell Biology, Genome Institute of Singapore, Singapore/Singapore,* [9]*Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore/Singapore,* [10]*Department of Cardiothoracic Surgery, National Heart Centre Singapore, Singapore/Singapore,* [11]*Clinical Pharmacology Laboratory, National Cancer Centre Singapore, Singapore/Singapore*

Background: EGFR mutant (M+) NSCLC is an archetypical oncogene-driven solid tumor, typified by high response rates when treated with a tyrosine kinase inhibitor (TKI), and median progression free survival of 10 months, commonly due to emergence of T790M. The genomic architecture and spectra of EGFR M+ tumours may provide insights to mechanisms of treatment failure and has not been well described to date. **Methods:** Paired tumor-normal exome/ transcriptome sequencing and SNP array was performed on 30 tbiopsies from 25 patients with TKI resistance (TKI-R) as well as multiple regions (n=46) of 8 treatment naïve (TKI-N), never smoker East Asian EGFR M+ NSCLC (L858R, n=5; exon 19 del, n=2; exon 20 ins, n=1). Genomic alterations were validated with targeted re-sequencing at a mean depth of 2000x. Alterations were identified and annotated using established pipelines. **Results:** Exome sequencing of 46 sectors (4-11 sectors/ tumor) from 8 resected NSCLC (Stage IA, n=5; Stage IB, n=3), revealed a median of 52.5 validated mutations (Range: 15-112) per tumor. Primary EGFR mutations (including exon 20 ins) were identified as truncal events in all cases, with the notable absence of T790M even at sequencing depths of 2000x. Private mutations comprised 10-33% of all mutations per tumor, and in some cases harbored potential drivers of subclonal diversity including p53, AKT1 and ATXN1. For the 30 TKI-R tumors (T790M+, n=16; T790M-, n=14), exome sequencing revealed a higher mutation burden (median 80 vs 49 in TKI-N), while SNP array and expression data confirmed ERBB2 and MET as common co-existing resistance mechanisms. We next inferred the relevance of alterations and their hierarchical order (trunk, T; branch, B; private, P). In a TKI-N tumor where 11 sectors were subject to exome-sequencing, 39 of 112 mutations were truncal events – with MAP3K19 and PTEN splice site mutations co-existing with EGFR L858R mutation. Strikingly, when comparing the transcriptomic profiles of TKI-N and TKI-R tumors, all 8 evaluated sectors in this tumor clustered together with the TKI-R signature, suggesting that truncal co-mutations can contribute to primary TKI resistance. Finally, we attempted to curate novel genes in the 46 TKI-N sectors that may be implicated in TKI resistance by identifying genes in common with those altered in TKI-R samples with allele frequency > 0.25. We shortlisted approximately 150 recurrent genes or putative drivers – 85% of which were either trunk or branch mutations including TP53 (T,P), PTEN (B), LRP1B (B), GPRIN3 (B), MAP3K19 (T), ARID3A (P) and MED12 (P). **Conclusion:** Multi-region sequencing of 8 never smoker EGFR M+ NSCLC revealed a low mutation burden, with a significant proportion of alterations occurring as trunk or branch events. The different activating *EGFR* mutations were ubiquitous truncal events and T790M was not found in ultra-deep sequencing across 46 sectors. Mutation hierarchy provides a basis for patterns of TKI treatment failure: with co-occurring truncal events (e.g. MAP3K19, PTEN) potentially contributing to primary resistance, and the low incidence of private subclonal drivers consistent with the relatively high prevalence of T790M mutation in the setting of secondary resistance. **Keywords:** Tumor heterogeneity, EGFR mutation, NSCLC, TKI resistance

PRESIDENTIAL SYMPOSIUM INCLUDING TOP 4 ABSTRACTS
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PLEN04.07 Stopping Smoking Reduces Mortality in Low-Dose Computed Tomography (LDCT) Screening Volunteers Ugo Pastorino[1], Roberto Boffi[2], Alfonso Marchianò[3], Stefano Sestini[4], Elena Munarini[2], Giuseppina Calareso[3], Mattia Boeri[5], Giuseppe Pelosi[6], Gabriella Sozzi[5], Mario Silva[7], Nicola Sverzellati[7], Carlotta Galeone[8], Arianna Ghirardi[9], Giovanni Corrao[9], Carlo La Vecchia[8] [1]*Thoracic Surgery, Fondazione Irccs Istituto Nazionale Dei Tumori, Milan/Italy,* [2]*Tobacco Control, Fondazione Irccs Istituto Nazionale Dei Tumori Milano, Milan/Italy,* [3]*Radiology, Fondazione Irccs Istituto Nazionale Dei Tumori, Milan/Italy,* [4]*Thoracic Surgery, Fondazione Irccs Istituto Nazionale Dei Tumori Milano, Milan/Italy,* [5]*Tumor Genomics, Fondazione Irccs Istituto Nazionale Dei Tumori, Milan/Italy,* [6]*Pathology and Laboratory Medicine, Fondazione Irccs Istituto Nazionale Dei Tumori, Milan/Italy,* [7]*Radiology, University Hospital of Parma, Parma/Italy,* [8]*Clinical Sciences and Community Health, University of Milan, Milan/Italy,* [9]*Statistics and Quantitative Methods, University of Milano-Bicocca, Milan/Italy*

Background: The National Lung Screening Trial (NLST) has achieved a 7% reduction in mortality from any cause with low-dose computed tomography (LDCT) screening, as compared with the chest radiography arm. Other randomized trials are under way, comparing LDCT screening with no intervention in heavy smokers populations. None of these studies is designed to investigate the impact of smoking habits on screening outcome. In the present study, we have tested the effect of stopping smoking on the overall mortality of volunteers undergoing LDCT screening. **Methods:** Between 2000 and 2010, 3381 heavy smokers aged more than 50 years were enrolled in two LDCT screening programmes. Sixty-nine percent were males with median age of 58 years and median smoking exposure of 40 pack-years. Based on the last follow-up information, subjects were divided in two groups: current smokers throughout the screening period, and former smokers. The latter group included ex-smokers at the time of baseline screening (early quitters), and those who stopped smoking during the screening period (late quitters).The effect of smoking on mortality was adjusted according to the following covariates: gender, age, body-mass index (BMI), lung function (FEV1 %) and pack years at baseline. **Results:** With a median follow-up time of 9.7 years, and a total of 32,857 person/ years (P/Y) follow-up, a total of 151 deaths were observed in the group of 1797 current smokers (17,846 P/Y) and 109 in 1584 former smokers (15,011 P/Y). As compared to current smokers, the Relative Risk (RR) of death of former smokers was 0.77 (95% CI, 0.60 to 0.99, p = 0.0416), corresponding to a 23% reduction of total mortality. Excluding 239 subjects who had stopped smoking from less than 2 years from the end-point of follow-up, RR was 0.64 (95% CI, 0.48 to 0.84, p = 0.0016), with a 36% mortality reduction. A similar risk reduction was observed in the subset of 476 late quitters (27 deaths, 4,777 P/Y), with a RR of 0.60 (95% CI, 0.40 to 0.91, p = 0.0158). **Conclusion:** Stopping smoking is associated with a significant reduction of the overall mortality of heavy smokers enrolled in LDCT screening programs. The benefit of stopping smoking appears

to be 3 to 5-fold greater than the one achieved by earlier detection in the NLST trial. **Keywords:** overall mortality, stopping smoking, LDCT screening, heavy smokers

EGFR WT AND MT TARGETING
WEDNESDAY, SEPTEMBER 9, 2015 - 16:45-18:15

ORAL32.05 EGFR IHC and FISH Correlative Analyses (SQUIRE Trial): Necitumumab + Gemcitabine-Cisplatin vs Gemcitabine-Cisplatin in 1st-Line Squamous NSCLC Fred R. Hirsch[1], Theresa A. Boyle[1], Nick Thatcher[2], Luis Paz-Ares[3], Marileila Varella-Garcia[1], Ashley A. Kowalewski[1], Rebecca R. Hozak[4], Gu Mi[4], Symantha A. Melemed[4], Charles W. Caldwell[4], Raffael Kurek[5], Mark A. Socinski[6] [1]*Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora/CO/United States of America,* [2]*The Christie Hospital, Manchester/United Kingdom,* [3]*Instituto de Biomedicina de Sevilla – Ibis (Hospital Virgen Del Rocío, Universidad de Sevilla & Csic), Sevilla/Spain,* [4]*Eli Lilly and Company, Indianapolis/IN/United States of America,* [5]*Lilly Deutschland Gmbh, Bad Homburg/Germany,* [6]*University of Pittsburgh, Pittsburgh/PA/United States of America*

Background: SQUIRE, a randomized phase III study, demonstrated that the addition of necitumumab (N) (a second-generation, recombinant, human immunoglobulin G1 EGFR antibody) to gemcitabine-cisplatin (GC) improved overall survival (OS) in patients with stage IV squamous non-small cell lung cancer (NSCLC). Analyses of the relationship between efficacy and epidermal growth factor receptor (EGFR) protein expression using the immunohistochemistry (IHC) H-score=200 cut-point were previously reported (Thatcher et al. Lancet Onc, 2015; doi: 10.1016/S1470-2045(15)00021-2). Here we report additional exploratory analyses of the relationship with EGFR protein, as well as analyses of EGFR gene copy number. **Methods:** SQUIRE included mandatory tissue collection from archived tumor. EGFR protein expression was assessed by IHC in a central lab, using the Dako EGFR PharmDx kit. Analyses of the relationships between efficacy outcomes with EGFR across the range of protein levels were performed, using methodologies including subpopulation treatment effect pattern plot (STEPP) with a sliding window target size of 200 patients. An exploratory assessment of EGFR gene copy number gain was performed in tissue sections using fluorescence in situ hybridization (FISH) (J Clin Pathol; 2009;62(11):970-7). Efficacy outcomes were estimated using the Kaplan-Meier method and hazard ratios estimated using an un-stratified Cox model. . **Results:** A total of 982 patients (89.8% of the ITT) had evaluable IHC assay results. The large majority of these patients (95.2%) had tumor samples expressing EGFR protein; only 4.8% had tumors without detectable EGFR protein (H-score=0). The STEPP analyses showed no consistent trend or obvious cut-point for the relationship between either OS or PFS with EGFR protein across the range of IHC values when comparing treatment arms. Archived tumor tissue with evaluable results for exploratory EGFR FISH analysis was available for 51.0% of patients (557 of 1093 ITT patients). Of these patients, 208 patients (37.3%) had increased EGFR gene copy number (FISH positive). A trend for greater necitumumab benefit was observed in EGFR FISH positive patients. Treatment HR (95% CI) for FISH positive and negative patients were 0.70 (0.52, 0.96) and 1.02 (0.80, 1.29) for OS, and 0.71 (0.52, 0.97) and 1.04 (0.82, 1.33) for PFS. However, the interaction of EGFR gene copy number gain with treatment was not statistically significant for either OS or PFS (p=0.066 and 0.057, respectively). **Conclusion:** The analysis of EGFR protein expression did not identify consistent trends related to efficacy outcomes across the range of IHC values. EGFR gene copy number gain showed a trend for a more favorable HR, but did not appear to be strongly predictive. However, both markers showed some evidence of potential trends that will be investigated further in future trials. **Keywords:** Necitumumab, correlative analysis, EGFR, SQUIRE

NEW KINASE TARGETS
WEDNESDAY, SEPTEMBER 9, 2015 - 18:30-20:00

MINI30.14 Evaluation of the MET/AXL Receptor Tyrosine Kinase (RTK) Inhibitor MGCD265 in a Patient with Metastatic Non-Small Cell Lung Cancer (NSCLC) Harboring AXL Amplification Khanh T. Do[1], Laura Macconaill[2], Adrian Dubuc[2], Isan Chen[3], Richard Chao[3], Vanessa Tassell[3], James Christensen[3], Geoffrey I. Shapiro[1], Lynette M. Sholl[2] [1]*1Early Drug Development Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston/MA/United States of America,* [2]*Department of Pathology, Brigham and Women'S Hospital, Boston/MA/United States of America,* [3]*Mirati Therapeutics, Inc., San Diego/CA/United States of America*

Background: MGCD265 is a spectrum-selective small molecule inhibitor of the AXL and MET receptor tyrosine kinases (RTKs). AXL and MET may be activated in NSCLC by gene mutation, amplification or rearrangement, resulting in oncogene addiction. Additionally, these RTKs are implicated in the progression of NSCLC and in acquired resistance to EGFR inhibitors. Although *AXL* genomic abnormalities have been reported in NSCLC, therapeutic targeting of such alterations with AXL inhibitors has not been clinically validated. Here we report the first documented objective response in a patient with *AXL*-amplified NSCLC with a small molecule AXL inhibitor. **Methods:** A 56 year- old male, never-smoker, was diagnosed with metastatic adenocarcinoma of the lung, with bilateral mediastinal lymphadenopathy and pleural carcinomatosis. Targeted next-generation sequencing (NGS) demonstrated *AXL* low amplification (estimated 5 copies), *CDKN2A/B* loss, *CCNE1* amplification, *AKT2* amplification and *MTOR* mutation (p.R132C). The tumor was wild-type for *EGFR*, *ALK*, *ROS1*, *RAS* and *MET*. He was treated with carboplatin/pemetrexed and bevacizumab, followed by docetaxel, with a best response of stable disease. Based on *CCNE1* amplification, he was also enrolled in a clinical trial combining an ATR inhibitor with cisplatin. His course was complicated by pneumonia and continued disease progression. A second biopsy was procured after initial chemotherapy, with targeted NGS demonstrating similar findings, but with high-grade *AXL* amplification (13 copies). IHC analyses also indicated MET expression (3+) and PD-L1 negativity. He was enrolled in the Phase 1b expansion portion of the Study 265-101 and was treated with MGCD265 at 1050 mg BID starting April 23, 2015. **Results:** The patient experienced rapid clinical improvement after treatment with MGCD265. He was oxygen-dependent prior to starting the trial and is currently able to bike 7 miles per day. Tumor imaging obtained after 2 cycles of treatment on June 2, 2015 showed a partial response (PR) with a decrease in index lesions of 42.3%, compared to baseline tumor imaging on April 22, 2015. The PR was confirmed after 4 cycles on treatment (July 14, 2015) with a decrease from baseline tumor imaging of 48.8% in index lesions. Other than Grade 1 diarrhea and AST/ALT elevation, he has experienced no other toxicities on study. **Conclusion:** To our knowledge, this is the first documentation of objective response of a NSCLC patient with *AXL* amplification treated with a small molecule inhibitor of AXL suggesting that *AXL* alterations may act as oncogenic drivers. Further study of MGCD265 in tumors with *AXL* genetic alterations is warranted.

